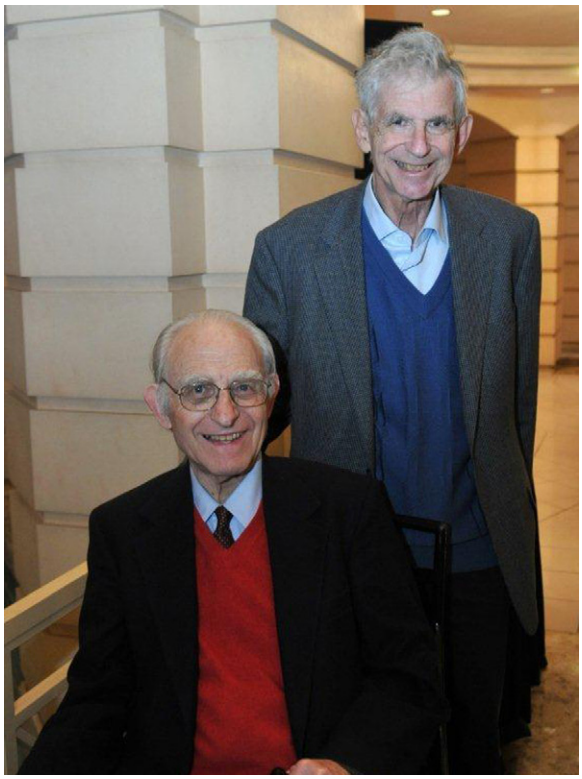
2010 Victor A. McKusick Leadership Award Introduction and Address

Arno Motulsky[1,*] and Charles J. Epstein[2,3]



Introduction by Arno Motulsky

An early version of these remarks was presented in San Francisco on March 30, 2010, when there was worry that Charlie might be unable to travel for the meeting in early November.

I am deeply honored and gratified to present the McKusick Leadership Award of the ASHG to Charles Epstein at this occasion. I have known Charles as a close friend and colleague for almost 50 years when, in 1963, he joined our relatively new Division of Medical Genetics at the University of Washington for a postdoctoral fellowship.

Charlie became a widely admired medical geneticist whose achievements fit perfectly the specifications for this award. He fostered and enriched the development of various medical genetics disciplines and exemplified enduring leadership and farsighted vision that ensured the field of human genetics flourish and be successfully assimilated into the broader context of science, medicine, and health. His multiple contributions to the understanding of human genetics by policy makers have been an additional important contribution.

Charlie contributed both to clinical genetics as well as to research genetics, and he became a model for physician-scientists. He forged and molded the specialty of human and medical genetics in many ways and thereby helped to create an essential place for our specialty in the basic and clinical medical sciences.

Charlie's undergraduate degree was in chemistry, and early in his career he spent some time at the NIH in Bethesda in Christian Anfinsen's laboratory, where he worked on protein chemistry and contributed to the body of work that brought the Nobel Prize to Anfinsen for showing that the three-dimensional structure of a protein was determined by the linear sequence of its amino acids.

During his fellowship in Seattle, Charles became interested in the recessive disease of Werner syndrome, suggesting its phenotype of premature aging as a potential model to study normal human aging. The condition was later shown to be caused by a mutant helicase, but the mechanism that produced the Werner syndrome phenotype and the role of this helicase in normal aging remains unknown. In fact, Charlie considers the Werner syndrome phenotype a caricature rather than a model of aging, but note that research on Werner syndrome continues elsewhere.

Charles' major research studies relate to Down syndrome and explain the mechanism of the human Down phenotype to the triplication of chromosome 21. Charlie and his colleagues were able to breed mice with segmental trisomy 16, which shared many genes identical to those triplicated on human chromosome 21 for gene dosage studies. He was able to use trisomy segmental chromosome 16 mice for understanding the human trisomy 21 phenotype. His wife, Lois, a physician-scientist, was an important collaborator in Charles' work on the mouse genetic model and much other work.

Note that, in 1986, when chromosomal abnormalities could be increasingly diagnosed, Charlie published a major monograph on the principles and mechanisms of

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[3]These remarks are published posthumously in loving memory of Dr. Charles Epstein, who passed away on February 15, 2011
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chromosomal imbalance. In addition to a research and diagnostic laboratory at the University of California in San Francisco, Charlie initiated a genetic clinic and established satellite clinics to bring genetic services and genetic counseling to outlying communities. Over 50 fellows and a large number of genetic counselors were trained.

In 2004, he, Bob Erickson, and Tony Wynshaw-Boris published a book on inborn errors of development.[1] This book was selected as the best book in clinical medicine by the American Association of Publishers. Between the years of 1987 and 1993, Charles was a superb principal editor of the *AJHG*, setting high standards and an example for his successors as editors of this prestigious journal.

Charles played an important role in setting wise policies for the ASHG, the American Board of Medical Genetics, and the American College of Medical Genetics, and was elected as president of all three bodies. As an important figure and symbol of human genetics as editor of the *AJHG*, Charles was attacked by the Unabomber in 1993 and almost died, but was left with residual damage in one extremity.

I know I speak for all human and medical geneticists at this meeting and elsewhere in telling you how much we respect, revere, and love you not only for your achievements in human genetics but for being a real "Mensch." We will now hear from Charlie about his reaction to this well-deserved award.

Address by Charles J. Epstein

November 4, 2010

Thank you very much, Arno, for your very kind introduction. I am greatly honored to receive the Victor McKusick Leadership Award of The American Society of Human Genetics and to share the platform with this afternoon's two other awardees, Gerald Fink, who just received the Gruber Genetics Prize, and Jurg Ott, the recipient of the Society's William Allan Award.

Victor McKusick, for whom my award is named and himself the 2008 awardee, and Arno Motulsky, who just introduced me and is the 2009 awardee, are generally regarded as the fathers of medical genetics in America. They transformed their interests in genetic diseases from being just sidelines of their medical specialties, cardiology and hematology, respectively, into what we recognize as medical genetics as we have come to know it. That they were able to do so came from the fortuitous convergence of their own visions of how genetics could be integrated into the practice of medicine and the explosion in scientific knowledge, both conceptual and technical, that were occurring at the time. Remember, those were days of the Watson-Crick model for the structure of DNA, of Jacob and Monod's theory of genetic regulation, of Tjio and Levan's elucidation of the true number of human chromosomes, of the discovery of several human disorders caused by aneuploidy, of the deciphering of the genetic code, and of the development of techniques for chromosome identification, paper electrophoresis, and column chromatography, just to mention just a few. Those were very heady times in science, and I was so fortunate to be starting my scientific career at that time.

My early career was blessed with the opportunity to work with many leaders in medicine and science, but two were the most influential. One, of course, was Arno Motulsky, from whom I learned how genetics and medicine intersected and what genetic counseling was and how it was conducted. In those days, genetic counseling was something that *physician*s and perhaps an occasional social worker did, a situation that was soon to change. My time with Arno was all too brief—less than a year—but his imprint on me was indelible! We accomplished a lot together, particularly on the elucidation of the clinical phenotype, pathology, and genetics of Werner syndrome[2] and on the first description of the fibrillin 2 disorder now known as congenital contractural arachnodactyly.[3]

My other mentor was Christian Anfinsen, a protein biochemist at the National Institutes of Health who won the Nobel Prize in Chemistry in 1972. I worked in Chris's laboratory for several years, with a year out in the middle to go to Seattle to study with Arno Motulsky. Anfinsen was interested in the problem of how the primary amino acid sequence of a protein determined its three-dimensional or tertiary structure. The first step in attacking this problem was to prove that it actually did, and it fell to me to carry out a series of experiments along these lines. It was while working on this problem that my nascent interest in human genetics was solidified. I say "nascent" because my initial interest in genetics was fostered by Kurt Benirschke, my pathology instructor in medical school. It was Kurt, who was very interested in cytogenetics, who called my attention to the report of Lejeune, Gautier, and Turpin describing the discovery of trisomy 21 as the cause of Down syndrome.[4] In any event, I saw the determination of the tertiary structures of proteins as a genetic matter, since it was the primary structures, the amino acid sequences, that were encoded in the genes. I articulated this thinking in one of my earliest papers, along with Bob Goldberger and Chris Anfinsen, entitled *The genetic control of tertiary protein structure*, of which I am still quite proud.[5]

Although Chris Anfinsen was a consummate experimentalist and seemed to be able to make anything in the laboratory work, his method of teaching was by *not* teaching. "This is what I want you to do," he said shortly after I arrived in his laboratory, and he then promptly left town and was gone for more than two months. After a brief period of helplessness, it became apparent that I had to figure out what needed to be done and how to do it by myself. It was an important lesson and became the model that I tried to use with my own postdoctoral trainees—encourage individual initiative and allow the trainee the pleasure of making his or her own discoveries. And, the more that I think about it, Arno employed the same strategy himself.

The danger of this approach is that some may fall by the wayside, but most of them did rise to the challenge.

Although I do not consider Victor McKusick as a mentor per se, I should mention, since this is the McKusick Award that I am receiving, that I did spend a very pleasurable half-day a week attending his Genetics Clinic conferences at Johns Hopkins while I was completing my time at the NIH. Given Victor's interests in connective tissue disorders—he had just published the third edition of his *Heritable Disorders of the Connective Tissue*[6]—I was able to broaden my clinical exposure to this group of conditions, as well as to many other rare entities that showed up in his clinic. I learned a lot about the lumping and splitting of genetic disorders, an argument that I believe has been put to rest by the discovery of the molecular bases of these conditions, which forms the subject matter of *Inborn Errors of Development*,[1] which I recently edited with Bob Erickson, a former research fellow, and Tony Wynshaw-Boris, my successor at UCSF.

Over the more than forty years that I worked at the NIH and the University of California, I was extremely fortunate to have been associated with a large group of research fellows, some fifty in all, many of whom have gone on to have spectacular careers in research. Although I was officially their mentor, I believe that in many ways they were the mentors and I was the student. I learned a tremendous amount from them, and they certainly kept me on my toes. I also interacted with another eighty or so clinical trainees who came through our program, and again I learned much from them about clinical genetics.

In the program for this meeting there is a statement that I "helped establish and legitimize the profession of genetic counseling in the late 1970s," and later on there is reference to my "gracious leadership of our professional community…in the mid-90s." What are these all about? The first statement refers, I believe, to my involvement with the Genetic Counseling Program at the University of California, Berkeley. This program was started in 1974, about five years after the Sarah Lawrence program began, and ceased operation in 2004. The UCSF Genetics Clinic served as the principal clinical training site for the Berkeley program throughout this entire time, and over a hundred counselors received training with us. In addition, we always had several genetic counselors working in our general, prenatal diagnosis, biochemical genetics, and satellite clinics, and one of these counselors was dedicated to the supervision of the Berkeley students. Our operating philosophy was that genetic counselors worked *with* rather than *for* the physician geneticists in the group, and there is no question that these clinics could not function without them. If any of this constitutes establishing and legitimizing genetic counseling, so be it, and I am very pleased to accept the accolade.

Now, what about my "gracious leadership in the mid-'90s"? This story begins thirty years ago when the American Board of Medical Genetics was spun off by The American Society of Human Genetics to deal with issues of training and competence in various aspects of clinical and laboratory genetics, including genetic counseling. The Board issued its first certifications in 1982, and then every two or three years thereafter. Unfortunately, although these certifications had credibility within the medical genetics community and served to upgrade the training and qualifications of geneticists and counselors, they had no standing outside of it. To the outside world of the AMA and its various affiliated organizations, we were a "self-designated board," one of some 100 to 150 certifying organizations, most of dubious merit. The only way for a certifying board to be regarded as legitimate is for it to be accredited by the American Board of Medical Specialties (ABMS for short), which was notoriously refractory to accepting new boards into the fold of organized medicine. Although unsuccessful attempts to gain entry into ABMS were made in the latter part of the 1980s, a window of opportunity opened up in 1991 and the American Board of Medical Genetics slipped in. It was the 24th primary board to be accepted and now, nearly twenty years later, it is still the last. But, this victory was not without its costs. As far as ABMS was concerned, its member specialty boards were supposed to be in the business of certifying physicians—and *only* physicians. PhDs and genetic counselors with master's degrees were not welcome. Through considerable negotiation, it was possible to keep the certification of PhDs within the Board of Medical Genetics—a not insignificant accomplishment, but the ABMS was intransigent when it came to genetic counselors, who did not possess a doctoral degree. It is not clear why this was so, since the American Board of Radiology was permitted to certify Radiologic Physicists who held either PhDs or master's degrees.[7]

Now, this is where the "gracious" part comes in. As the then President of the Board, it fell to me to go to persuade the diplomates that it was in the best interests of all to split the Board into two separate boards, one comprised of the MDs and PhDs that would be recognized by ABMS, and the other, for the genetic counselors, that would not. This persuasion consisted of an editorial in *The American Journal of Human Genetics*, of which I was then the Editor, and of an open forum at the annual meeting of The American Society of Human Genetics, which I was obliged to lead, at which the proposal was discussed. It was not a very comfortable place for me to be. Being split off from the Board of Medical Genetics would be a bitter pill for the counselors to swallow, and many dire consequences of the separation were predicted. However, it would have been even worse if the Board was not split and remained outside of ABMS. As I wrote in the 1992 editorial, we had been given the rare opportunity to become a recognized and legitimate medical specialty, with all that that entailed, and this opportunity was not likely to come again.[8] The times were tense, and indeed everyone, not only I, had to be gracious to prevent a fracturing of the medical genetics community and the creation of adversarial relationships that would indeed have been

disastrous. A two-thirds majority of the diplomates was required to approve the split, and the genetic counselors comprised nearly 40% of the diplomates.[9] But graciousness did prevail, and the Board was split. Now, nearly twenty years later, the American Board of Genetic Counseling, the National Society of Genetic Counselors (NSGC)—the counselors' equivalent of the American College of Medical Genetics—and the genetic counseling community in general are thriving, and what happened in the '90s is just ancient history.

There is a certain irony in thinking about the many leadership positions in human genetics that I have held. My training in college was in chemistry, my postdoctoral work—the time I spent at the NIH—was in protein biochemistry, and my research at the University of California was on early embryonic development, X chromosome inactivation, mouse models of Down syndrome, the superoxide dismutases, and the role of oxygen free radicals in aging. All of this, I would submit, was pretty hard science. By contrast, my clinical training in genetics was quite modest and would be considered inadequate by current standards. I was largely self-trained, with the help of our many trainees and counselors and of the two outstanding dysmorphologists in our group, Bryan Hall and Mahin Golabi. As a result, despite my administrative responsibility for the operation of the UCSF Genetics Clinic and our clinical training program, I must confess that I never considered myself as a *real* clinical geneticist. So, what leadership positions was I given? President of the American Board of Medical Genetics, President of the American College of Medical Genetics, and Chairman of the Residency Review Committee for Medical Genetics—the three major elements of the clinical genetics establishment, and I have never regretted a minute of my service to any of these organizations. Thank you all for giving me the opportunity!

I made passing mention earlier of the book, *Inborn Errors of Development*, but I did not mention its subtitle: *The Molecular Basis of Clinical Disorders of Morphogenesis*. For me, this book represents the ultimate coming together of the basic science with the clinical, of developmental genetics with dysmorphology. Although I had long dreamed of writing such a book, it was not until recently that it became possible to do so – not by myself but with two coeditors and some 400 contributors. The science is finally catching up to the clinic.

In closing, I would like once again to thank The American Society of Human Genetics for awarding me this recognition, all of you for your support, and my wife, Dr. Lois Epstein, and our children and their families, for all of their love and support during good times and bad. I have been truly blessed!

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